April 18, 1997

On March 21, 1995, the Food and Drug Administration (FDA) held a public workshop entitled "Positron Emission Tomography (PET) Regulatory Workshop." During the course of the workshop, many members of the audience asked questions about a variety of issues related to the regulation of PET drug products. On October 24, 1996, the FDA issued the first of a series of answers addressing these questions.

In addition, on October 27, 1996, representatives from the Food and Drug Administration (FDA) participated in the Eighth Annual International PET Conference organized by the Institute for Clinical PET to provide further guidance on the regulation of PET products. A set of questions was presented to the FDA representatives at this workshop.

In an effort to address questions raised at the March 21, 1995, and October 27, 1996, workshops, staff members in the Offices of Generic Drugs, Pharmaceutical Science, Compliance, and Review Management in the Center for Drug Evaluation and Research and staff from the Health Care Finance Administration (HCFA) have developed answers (see attached).

The FDA understands that questions about the regulation of PET products will continue. Therefore, the Agency is undertaking additional efforts to facilitate the dissemination of information on PET drug products to industry and the public. Planned activities include a second public workshop on April 28, 1997, and several guidance documents.

For further information contact:

Susan Lange
Regulatory Health Project Manager
Office of New Drug Chemistry
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857
(301) 443-0260

April 18, 1997

Guidance for Industry[1]

Pet Questions and Answers

Questions for FDA from March 21, 1995 Workshop

Q1: What will happen when an ANDA is submitted and there is ongoing clinical activity for the drug at that site?

A: Under these circumstances, FDA does not intend to prevent the use in clinical practice unless a safety problem is identified. FDA does not intend to take regulatory action against any PET facility during the preparation and FDA review of an ANDA if the facility demonstrates a good faith effort to comply with FDA regulations by developing a well-designed written plan or procedure with reasonable and defined time frames.

Q2: If we were working under PRC, would we be classified as a drug manufacturer?

A: We would not expect a person who owns or operates a PET facility to register as a drug manufacturer if the facility is only doing PRC work (i.e., limited solely to physiological research) and/or investigational clinical trials, not for sale and is not selling the drug product.

Q3: Are facilities that manufacture PET radiopharmaceuticals for (a) purely physiological research, (b) investigational clinical trials, required to register as a drug manufacturer?

A: Generally, persons who own or operate establishments that manufacture PET radiopharmaceuticals must register with FDA in accordance with section 510 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360, and FDA regulations. However, owners or operators of PET facilities may be exempt under § 207.10(d) if they manufacture PET radiopharmaceuticals solely for use in purely physiological research and/or investigational clinical trials, and not for sale.

---

[1]This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on PET products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and/or regulations.

Q4: Did FDA intend that PET Regulatory Committees (PRC) would have a broader mandate than Radioactive Drug Research Committees (RDRC)? What is the relationship between PRCs and RDRCs?

A: FDA proposed the concept of a PRC in response to requests from the PET community for a committee devoted specifically to PET. As described in the guidance document [60 *FR* 10594], much of the guidance on the operation of a PRC is identical or very similar to the RDRC requirements in 21 CFR 361.1. FDA did not intend that PRCs would have a broader mandate than RDRCs.

FDA is planning to publish a proposed rule amending 21 CFR 361.1 to update and clarify the requirements for radioactive drug products for basic research. If this proposal is finalized, the need for separate PRCs for PET radiopharmaceuticals will be eliminated.

Questions from Institute for Clinical PET October 27, 1996 Workshop

Q5: What triggers a compliance inspection at a PET center between now and when their ANDA is filed?

A: Generally, FDA performs GMP inspections for drug manufacturing facilities every two years and in advance of approvals for NDAs and ANDAs, changes in plant layouts or manufacturing operations or procedures, consumer complaints, reports of adverse reactions, and product recalls. When there are questions or concerns regarding public health or product safety, FDA may inspect any manufacturing facility or institution at any time.

Q6: Does FDA intend to inspect PET center manufacturers using a local compliance inspector or will an "expert" PET inspector be involved?

A: FDA intends to inspect PET center manufacturers using a "team approach," involving local FDA field investigators, personnel from CDER (primarily, a chemist and a manufacturing compliance officer), and other FDA personnel as needed. FDA intends to ensure that people with the necessary expertise are involved in PET inspections.

Q7: In the Memorandum Opinion of the U.S. District Court of the District of Columbia. (Section IV.B.2., page 22) Judge Sullivan states "The FDA has not made a blanket decision to enforce the FD&C Act against all PET manufacturers without exception." What are the criteria FDA will use to decide whether or not to enforce the Act at a specific PET site?

A: FDA has limited enforcement resources and does not intend to initiate an enforcement action against a PET manufacture for minor violations. FDA expects PET manufacturers to voluntarily comply with all applicable requirements. The agency intends to engage in dialogue with the PET community and to provide appropriate

guidance to bring PET manufactures into compliance. In exercising its enforcement discretion, the agency considers a wide range of factors depending on the facts of each individual case. Nonetheless, among the factors likely to be considered in this highly fact-specific endeavor are: (1) the public health significance of the violations and (2) the persistence, as well as the pervasiveness, of the violations observed.

Q8: Since it seems that FDA will selectively enforce the FD&C Act on PET Centers, will distribution throughout a university system (multiple hospitals) be a situation that might prompt an enforcement inspection?

A: Normally, the type of distribution system would not prompt an inspection. However, routine facility inspections are conducted periodically at all facilities. See the response to question 5 above regarding when such inspections are normally conducted.

Q9: Same question, only for a regional distribution outside a university system (i.e., commercial distribution throughout a geographic region, including across state lines).

A: See response to question 8, above.

Q10: Are any areas of CGMP, either implicitly or explicitly, excluded from requests for exemption?

A: No. We will accept properly justified requests for exceptions or alternatives to any CGMP provision.

Q11: In the case of FDG, please clarify the interrelationship between the NDA, DMF (clinical and chemistry) and ANDA.

A: An NDA containing data that established the safety and efficacy of FDG was submitted for premarket approval. Such an application could contain original clinical safety and efficacy data and CMC information or refer to data from other sources such as another NDA or DMF. If an applicant wants to conduct clinical studies of an indication not previously approved, an IND should be submitted to cover the studies for safety and efficacy. Submission of a new NDA or supplement to an already approved NDA or ANDA should then be submitted for approval of the new indication. Any other applicant seeking approval for the FDG product (i.e., same strength, dosage form, indications, and route of administration) may submit an ANDA.

Because an ANDA is based on the determination of safety and efficacy that was established when the agency approved the NDA, no "clinical" data is needed in an ANDA. Therefore, a reference to a DMF containing clinical data would not be necessary.

A DMF may be referenced for certain information that is to be included in the

chemistry section of the ANDA. If certain confidential information required for approval cannot be provided by the applicant in the ANDA, a reference to a DMF, supported by a letter of authorization from the holder of the DMF, can be used to supply the information.

Q12: What is the mechanism for applying for CGMP exemptions/alternatives?

A: PET manufacturers applying for CGMP exceptions or alternatives should submit a citizen petition to the Dockets Management Branch, Food and Drug Administration, Department of Health and Human Services, rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857. The phrase "PET Request for Exception or Alternative" should be clearly marked on both the envelope and the petition. The requirements for a citizen petition, and a template for a petition, are provided at 21 CFR 10.30.

Requests for an exception or alternative may be submitted by individual PET manufacturers, trade associations, or a group, as long as the facts presented are sufficiently individualized for each manufacturer seeking the exemption or alternative. FDA believes it is necessary to review individual requests to determine whether exceptions or alternatives are consistent with the basic principles of the CGMP regulations.

Q13: What information does FDA consider fundamental to a properly prepared request for CGMP exemptions/alternatives?

A: The specific information that should be submitted depends upon the nature of the request. A request for exception or alternative should include the following: (1) an explanation, with supporting data as necessary, of why compliance with a particular part of the CGMP regulations is unnecessary or cannot be achieved; (2) a description, with supporting data as necessary, of alternate procedures or controls that satisfy the purpose of the CGMP requirement; (3) other information justifying an exception or alternative. Relevant supporting information might include the radiological risks to personnel or patients, the manufacturing characteristics of the PET center, such as size, scale or capacity of equipment, number of lots per day and number of containers per lot, number of personnel, and the characteristics of the product including its packaging.

Q14: Under what conditions will clinical indication supplements allow other ANDA holders to include the new indications?

A: An ANDA for a product contains all of the indications approved in the NDA for the product unless covered by exclusivity. New indications may be afforded market exclusivity for a period of three years if clinical studies were essential to approval of the new indication. During the period of exclusivity, no other application holder would be permitted to include this indication in its labeling, unless they conducted full safety and efficacy studies for the desired indication. Once exclusivity, if any, expires,

ANDA holders should submit labeling supplements to change their labeling to match that approved in the NDA.

Q15: What activities (i.e., in-house use, regional distribution) might be allowed during the preparation of an ANDA, facility development, and procedure validation?

A: Refer to the answer to question 1.

Q16: Would a PET manufacturer be required to monitor and/or enforce any element of "off-label" use by prescribing physicians?

A: Although PET manufacturers are prohibited from directly or indirectly promoting any off-label use, they do not have an affirmative obligation to monitor or prohibit off-label use by prescribing physicians. However, each applicant having an approved NDA or ANDA is required to report adverse drug experiences obtained or received from any source (21 CFR 314.80), including adverse reactions to off-label uses of the drug. In addition, with regard to studies of off-label uses of its approved products, the applicant is required to include in its annual report to FDA any published clinical trials on "new uses." 21 CFR 314.81(b)(2)(vi).

Q17: Please clarify a physician's authority to prescribe off-label uses of approved drugs. Do you need to file an IND for such uses?

A: FDA's policy on "off-label" use of marketed drugs and biologics has been stated by the Office of the Associate Commissioner for Health Affairs. In the FDA's Information Sheets for Institutional Review Boards and Clinical Investigators, on Page 61, it states the following:

"Good medical practice and patient interest require that physicians use commercially available drugs, and biologics according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a product in this manner as part of the 'practice of medicine' does not require the submission of an Investigational New Drug Application (IND) or review by an Institutional Review Board (IRB), unless such review is required by the institution at which the product will be used."

"FDA encourages the submission of applications containing the relevant safety and effectiveness information on drugs and biologics being prescribed for 'off-label' uses. The Agency believes that it is important for appropriate uses to become part of the approved labeling so that patients may benefit from reliable and up-to-date information about the safe and effective uses of such drugs and biologics."

Furthermore, regarding investigational use of marketed drugs and biologics, the policy states:

"Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND is generally required. According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug, however, does not require an IND if:

(1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

(2) it is not intended to support a significant change in the advertising for the product;

(3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(4) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and

(5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7].

For additional information on whether or not an IND is required in a specific situation, contact:

Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-5818

The FDA's Information Sheets for Institutional Review Boards and Clinical Investigators from the Office of the Associate Commissioner for Health Affairs can be found on the World Wide Web: http://www.fda.gov/oc/oha/toc.html.

Q18: Can diagnostic agents (radiopharmaceuticals) be placed on a "fast track" for approval such as therapeutic agents? How could we make this happen?

A: The Center for Drug Evaluation and Research, Manual of Policies and Procedures (MAPP 6020.3), *Priority Review Policy*, April 22, 1996, describes the Center's priority review policy. Accordingly, an NDA receives priority review when "the drug product, if approved, would be a significant improvement compared to the marketed products (including non-"drug" products) in the treatment, diagnosis, or prevention of a disease." Generally, ANDAs are not significant improvements compared with marketed products, therefore, they would not be placed on a "fast track" review process. This policy also describes how this significant improvement may be demonstrated.

Q19: How does the FDA view the association of a PET center with a commercial partner for marketing and distribution? Is it a positive or negative factor?

A: FDA has no position on commercial marketing arrangements between application holders and distributors.

Q20: Please clarify whether percent yields of FDG below the established action limit are cause for batch rejection.

A: The drug product may be released if all the established release specifications are met (radiochemical purity, chemical purity, etc). Action limits are not batch release criteria. Action limits for percent yield are established in the master production record for a particular set of conditions for the manufacture of a drug product. At the conclusion of manufacturing of each lot, theoretical and actual yields are compared. If the actual percent yield falls outside the specified upper or lower ranges, an investigation should be conducted to identify the possible cause(s). The investigation should be documented in writing in a "manufacturing deviation report."

For example, a PET Center establishes specified upper and lower acceptable "percent yields" at 85% to 35% for the production of [^{18}F]FDG. The product's acceptability and conformance to approval criteria between these percentages have been documented and the method of production validated. Following production of a batch of [^{18}F]FDG, the yield percentage is calculated accurately at 29.7% (outside the acceptable range of "percent yields").

Release content testing (e.g., radiochemical purity, radiochemical identity, specific activity, total activity, radionuclidic purity, radionuclidic identity, chemical purity, and pH) as specified for the conditions of release for this lot of [^{18}F]FDG may be conducted and even completed.

Q21: Please clarify whether batch volumes of FDG below the established action limit are cause for batch rejection.

A: Volume is not a release criteria. See response above.

Q22: Please clarify if HPLC is required as a final product quality control of FDG.

A: HPLC is not required for final product quality control. However, suitable validated analytical methods to monitor the identity, quality, purity, and strength of the drug product should be conducted.

Q23: For ANDA applicants, please clarify whether critical raw materials from different suppliers must be qualified through complete stability studies. How many runs are necessary.

A: For applicants submitting an ANDA with multiple suppliers:

(a) for the starting materials, oxygen-18 enriched water, fluorine-18, and mannose triflate, information related to one batch using the material from each supplier including a stability study, should be submitted in the application. In addition, a Certificate of Analysis (CoA) from the supplier and your own CoA (tests and specifications) should be provided.

(b) of raw materials, inactive components, reagents and/or solvents should provide each supplier's CoA, and the name and address of the supplier.

For applicants with an approved ANDA, who want to change a supplier:

(a) for a starting material, information related to one batch using the material from the new supplier, including a stability study should be submitted in a prior approval supplement.

(b) of raw materials, inactive components, reagents and/or solvents, should submit the supplier's CoA, and the name and address of the new supplier in the annual report.

Q24: For ANDA applicants, please clarify whether different batch sizes must be qualified through complete stability studies. How many runs are necessary?

A: For approval of an ANDA, chemistry, manufacturing, and controls data, including stability data, from one batch should be submitted. ANDA holders should maintain documentation from three validation batches postapproval. A batch is defined as one production run (see question 26 for further definition). Where a 60 minute irradiation time is employed, a single stability batch will suffice. Where a range of irradiation times are employed, three additional batches of the drug product manufactured at the upper end should be studied.

Q25: Regarding other PET tracers (i.e., C-11, N-13, O-15, F-18) --
a. How do you envision bringing them into the regulatory stream?

b. A realistic estimate of time for extending the regulatory umbrella?
c. Any acknowledgment for the comparatively limited utility of such products?

A: a. Use of PET radiopharmaceuticals should be through the RDRC, IND, NDA, or ANDA process.
b. FDA had requested that the manufacturers of PET radioactive drugs comply with the law and expects an earnest effort from PET manufacturers to comply with the Federal Food, Drug, and Cosmetic Act to avoid any compliance action.
c. We acknowledge the limited utility of short lived PET radioisotopes (i.e., C-11, N-13, O-15, and F-18) as part of PET radiopharmaceuticals, however, these drugs should still meet safety and efficacy requirements.

Q26: Please clarify the FDA's perspective of what constitutes a batch of a PET radiopharmaceutical, especially with regard to those containing the shorter-lived nuclides 0-15 and N-13.

A: 21 CFR 210.3(b)(2) defines a "batch" as "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture." Therefore, in the case of PET radiopharmaceuticals, the material produced during a single irradiation cycle using the same synthesis and/or purification operation would constitute a batch.

Q27: How does the PET RDC fit within the scope of FDA's plans to regulate PET agents?

A: FDA is considering proposing changes to the regulations affecting all research with radioactive drugs conducted under an RDRC. Under these proposed changes, the need for a separate PRC for research with PET radiopharmaceuticals would be eliminated.

Q28: To what extent is FDA prepared to receive IND applications for other PET radiopharmaceutical (O-15 water, N-13, ammonia, F-18 fluoroDOPA, C-11 methionine, etc.)?

A: FDA is fully prepared to review the drug applications submitted by the sponsors.

Q29: If a PET facility (that currently produces FDG under an IND) wants to expand the indications for FDG what are the requirements to demonstrate equivalence between the FDG produced by the IND holder and that produced under the NDA?

A: Adequate and well controlled studies demonstrating the safety and effectiveness of the drug should be conducted and submitted for approval of any new indication

Q30: Given the varying production quantities of FDG (in mCi), does FDA intend to limit the distribution of the product only to either the final product container or unit-dose

containers?

A: Under 21 CFR § 314.93(b), if the strength of a drug product submitted for approval under an abbreviated new drug application (ANDA) differs from the approved strength of the reference listed drug (RLD), it is necessary to file a suitability petition before filing the ANDA. See 21 CFR § 314.93(c). Generally, a change in the concentration or total volume of a parenteral drug product will constitute a change in strength. The labeling for the RLD for Fludeoxyglucose F18 ([^{18}F]FDG) Injection designates a total volume of 16 ± 3 mL of isotonic saline (plus the requisite amount of [^{18}F]FDG. Therefore, an [^{18}F]FDG drug product submitted for approval under an ANDA should indicate the same total volume specified by the RLD labeling (13 - 19 mL), unless a suitability petition has been approved addressing the change in total volume (i.e., strength).

Q31: Could you describe the role of the PET Research Committee in physiologic research studies? Specifically, please discuss the issues regarding studies where injection in a human has not yet occurred. Is the issue pharmacologic effect? Also, what about compounds that have been used in humans without difficulty and are only minimally modified (a chemical analog) with no change in pharmacologic potency?

A: See response to question 27 regarding the role of PET Research Committees.

Q32: The USP has monographs for many PET tracers (about 8 or 9). Do these have any application in the FDA process?

A: Under section 501(b) the Federal Food, Drug, and Cosmetic Act, unless FDA adopts alternative standards, the USP monographs contain the standards for identity, strength, quality, and purity the drug products for which monographs are available. NDA or ANDA applicants for products covered by USP monographs should demonstrate in their applications that their products meet these standards.

Q33: Assuming that new indications for FDG require an IND, would the FDA consider allowing reasonable patient charges for the cost of the drug/imaging procedure (this is generally denied). In other words, is it possible to charge for investigational studies under an IND? If so, how does one go about this?

A: Under FDA regulations, 21 CFR 312.7, the investigator may request permission to charge for the drug supplied in the investigational studies. A letter requesting permission with a detailed explanation of the reason why it is necessary to charge would be sent to the review division.

Q34: I understand that CGMP's apply to the production of any drug for human use, regardless of whether the drug is produced under IRB, RDRC (PDRC), IND, ANDA, or NDA. I also understand that production facilities operating under ANDAs and NDAs

are legally required to undergo periodic CGMP inspections (every two years?). I further understand that any facility is subject to a CGMP inspection in the event of questions related to public health and safety. First, is my understanding of these issues correct? If so, do legal requirements exist for the periodic CGMP inspection of production facilities operating under IRB, RDRC (PDRC), or IND? If there are no legal requirements, how often is a production facility operating under IRB, RDRC (PDRC) or IND inspected for compliance with CGMP?

A: The CGMP regulations (21 CFR Parts 210 and 211) contain the minimum standards for preparation of drug products for administration to humans. CGMP inspections for manufacturing facilities are based on preapprovals for NDA/ANDA, changes in plant layouts, or in manufacturing operations or procedures, consumer complaints, reports of adverse reactions, and product recalls.

Currently, FDA performs preapproval CGMP inspections for the submission of NDAs and ANDAs and generally, routine CGMP inspections are performed every two years after final approval. Any facility that manufactures drugs for human use should be in compliance with the CGMP regulations. The FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal) dated March 1991 provides guidance on CGMP requirements for investigational new drug (IND) applications. CGMP inspections for IND applications are conducted on about one percent of all applications. Generally, these inspections are "for cause" due to potential problems or concerns regarding product safety. Any drug manufacturing facility is subject to a CGMP inspection in the event of questions related to public health and safety.

Manufacturing practices and standards for radioactive drugs for certain research uses, under 21 CFR Part 361.1, are evaluated during FDA inspections of an institution's RDRC.

Q35: Do good laboratory practices (GLPs) pertain only to animal pharmacology studies, or are GLPs also relevant to other areas (e.g., quality control procedures on the final drug product)? To me as a chemist, "laboratory" means a chemical research area, a production area, or a QC testing area. Do GLPs apply to these areas?

A: Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58, is intended to assure the quality and integrity of safety data for certain animal studies. CGMP regulations, as described in 21 CFR Parts 210 and 211, pertain to the preparation of drug products for administration to humans or animals. If chemical research areas, production areas, or QC testing areas participate in the preparation of drug products for administration to humans or animals, then these areas and their activities should operate in compliance with CGMP regulations.

Q36: To alleviate confusion between the FDA and the PET community, should ANDA applicants withhold submission of their applications until after the recently announced

1997 FDA workshop? What guidance can you provide applicants who have already filed ANDAs with OGD?

A: No. FDA has announced on several occasions that it is ready to receive ANDAs. As stated at the recent ICP meeting, FDA is developing a guidance document for the submission of ANDAs, with particular information for Fluorodeoxyglucose - F18 Injection, that should assist applicants who are preparing ANDAs for submission to FDA. If an application has already been submitted to OGD, it will be reviewed but can be amended to correct deficiencies.

Q37: Let's assume that an analytical method has been validated in an NDA. If an ANDA applicant uses the same analytical method as in the NDA, must the methods validation be repeated, or are system suitability tests (replicate injections, peak tailing, theoretical plates) sufficient? If an ANDA applicant uses a USP compendial analytical method, must the methods validation be repeated, or are system suitability tests (replicate injections, peak tailing, theoretical plates, etc.) sufficient? What changes to a method (supplier or equipment, detector, flow rates, solvents, supplier of standards, etc.) necessitate a revalidation of the method?

A: If the applicant is using a USP method, system suitability data are acceptable, per USP < 1275 > and methods validation data would not be required.

If the applicant is not using a USP method, the applicant must provide methods validation data to support approval of its ANDA (21 CFR 314.50(d)(1)(ii)(*a*)), although the methods validation data may be provided by reference to data in an NDA if the NDA holder authorizes the ANDA sponsor to rely on its validation data for submission in the ANDA. If any changes are made to the approved analytical methods, the revised method should be revalidated.

Questions for HCFA from March 21, 1995, Workshop

Q38: Why should radiopharmaceuticals be the only drugs that get approved by the FDA but then have to go through an additional level of review of Medicare coverage for the indicated uses, for labeled uses?

A: The one difference here is that this is a drug for diagnostic purposes rather than therapeutic, it is used in combination with a diagnostic technology and competes with a variety of diagnostic technologies that may or may not provide similar imaging.

From HCFA's point of view, PET scanning involves the use of both a device and a drug as a diagnostic tool. We are interested in whether something is safe, whether it does what it is supposed to do, and how well it does what it is supposed to do. How does it compare with other alternatives? What are the appropriate uses? And if we can find out, if we have the information available to us and the analytical capability, what is the relative cost

effectiveness compared to the alternatives?

Q39: Recognizing that private insurers and CHAMPUS have agreed to reimburse for PET, what can you say that you could do in the context of the promotion of the public health for the Medicare population and the population in general, as well as the protection of the public health?

A: We consider it a responsibility to assure our beneficiaries appropriate and effective health care. We now see the value of being able to move more quickly even if not with global decision, to make coverage decisions more quickly, to get ahead of the technology assessment curve and to be able to make coverage decisions more quickly even at a limited basis and then expand them as we get more information.

Q40: As well as demonstrating that PET is safe and clinically effective, if promoted, it could be proven to be cost-effective. What are you doing in the promotion part? We suggest an interim reimbursement policy to allow us to demonstrate that PET is truly not only safe through the FDA route, but also is cost-effective.

A: Using axillary lymph node imaging as an example, is the data robust enough to base a decision on -- a decision that will affect a population as large as the American female population with breast cancer? Is a study of 50 patients sufficient to promote the indication? Well-planned clinical trials can help answer the questions of safety and efficacy. The agencies have learned a lot during the PET evaluation process. HCFA might be able to start planning approvals after FDA approval for limited sites to start using the technology and return data to us and FDA and AHCPR to see if broader coverage is warranted.

Q41: Following FDA approval of a drug, could individual carriers make decisions for coverage as an interim policy?

A: It is undecided at this point whether an interim policy could be instituted. It will have to be discussed internally.

Q42: FDA approval of an NDA is necessary but not sufficient grounds for HCFA approval. Does that mean that a study conducted under and IND would never be eligible for HCFA approval?

A: Correct, IND studies and off-label indications would not be approved by HCFA.

Q43: Would a drug that has an NDA approval, but is being used for off label indications be approved for reimbursement by HCFA?

A: The reimbursement for off-label uses of a drug can be left to individual carriers to decide, and their policies may differ. HCFA could make a decision for national coverage policy if

it considered by HCFA to be needed at the time.